Should Patients with Medullary Thyroid Carcinoma Undergo Extensive Lymph Node (Re)Operation to Improve Long-term Survival?

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To investigate the role of primary and/or secondary modified radical neck dissection (MRND) in patients with medullary thyroid carcinoma (MTC), follow-up data on 43 patients operated on between 1972 and 1983 were analyzed retrospectively; patients included 16 with sporadic MTC (group 1) and 27 with multiple endocrine neoplasia type 2 (group 2). Primary surgical therapy consisted of (near-) total thyroidectomy and limited lymph node dissection; one patient in group 1 and two in group 2 underwent primary MRND. Positive nodes were found in nine patients of group 1 and in 12 of group 2. Calcitonin (CT) was raised postoperatively in 11 group 1 patients, who all died (four after additional MRND). Postoperative CT was normal in the four survivors of group 1. In group 2, postoperative CT was raised in 15 patients, including those who had MRND and in four apparently node-negative patients. Three of them underwent additional MRND, which was successful in one case. One patient in this group died of the disease; two patients developed elevated CT levels during follow-up, whereas in one, CT normalized spontaneously. In conclusion, the role of extensive lymph node surgery in patients with more than limited lymph node involvement or elevated postoperative CT levels remains to be established. (Henry Ford Hosp Med J 1992;40:271-5)

Medullary thyroid carcinoma (MTC) may occur as a part of multiple endocrine neoplasia (MEN) type 2A or 2B, as well as in sporadic nonhereditary cases. This carcinoma arises in the parafollicular C-cells that produce calcitonin (CT), which provides an excellent parameter for follow-up.

The primary treatment is surgical with general agreement that a total thyroidectomy should be performed. However, questions have been raised regarding the type of lymph node dissection which should be utilized: several authors (1-3) advise primary elective modified radical neck dissection (MRND); others disagree, arguing that MRND can never be radical (4), or does not improve prognosis (5), and that central neck dissection suffices (6-8). In addition, MRND is more mutilating and time-consuming than only removing the regional lymph nodes. However, most authors agree that MRND or even radical neck dissection (9) is mandatory if cervical lymph nodes are found to be positive (8,10-13). By meticulous microdissection of nonpalpable lymph nodes, a secondary MRND can lead to normalization of CT levels even several years after primary operation (14).

Would it not therefore be possible to do only limited lymph node surgery, i.e., clearance of the central neck area, at primary operation and reoperate on those patients whose CT levels remain high postoperatively?

To answer this question we reviewed our own patient material with the aim to 1) identify a subgroup with normal CT values postoperatively who did well without MRND, 2) see whether additional MRND was useful in patients with elevated CT, and 3) look at the course of the disease of those with elevated postoperative CT levels who were not reoperated on.

Patients and Methods

The records of all 43 patients with histologically proven MTC—16 with sporadic disease (group 1), 24 with MEN 2A and 3 with MEN 2B (group 2)—who were operated on between 1972 and 1983 were reviewed for information about age at diagnosis, tumor status, lymph node metastasis, type of thyroid and lymph node surgery, clinical course, survival, and CT values immediately postoperative and during follow-up.

Patient characteristics are shown in Table 1. As there were few patients with the MEN 2B syndrome, the results of the MEN 2A and MEN 2B patients were combined. A comparison was made between the group with sporadic disease and the group with hereditary MTC.

All patients received surgery, but the type of operative procedure varied. In group 1, at first operation a hemithyroidectomy was performed three times and a (near-)total thyroidectomy six times. In two patients the operation was not radical and in five patients only a biopsy was taken. After histological diagnosis of MTC, some patients were reoperated on. This finally resulted in 13 (near-)total thyroidectomies in this group and three nonradical operations. Lymph node surgery consisted of taking out the pre- and paratracheal (central) nodes, as well as limited dissection picking out suspicious-looking nodes in the lateral and me-

Table 1
Patient Characteristics

	Group 1	Group 2	
	Sporadic MTC	MEN 2A	MEN 2B
Number of patients	16	24	3
Sex (M:F)	7:9	12:12	0:3
Age at diagnosis (yrs)	58 ± 14	24 ± 13	
CT level at presentation			
elevated	12	20	
unknown	4	2	
normal (converters)*	—	5	
Tumor stage			
unilateral			
< 1 cm		4	
> 1 cm	10	—	
bilateral	2	21	
locally invasive	4	2	
Lymph node stage			
none	7	16	
homolateral	2	7	
bilateral	3	4	
fixed/extraregional	4	—	

*Operated on after conversion to elevated CT levels.

Table 2
Type of Primary Lymph Node Surgery in Relation to Postoperative CT Level

	Group 1		Group 2	
	CT Normal	CT Elevated	CT Normal	CT Elevated
Biopsy only	—	4*	1	—
Pre- and paratracheal nodes	4	4†	9	4‡
Picking out homolaterally§	—	1	1	4‖
Picking out bilaterally§	—	1	1	2‖
Extended regional	—	1	—	3
MRND	1	—	—	2
Total	5	11	12	15

*Three patients underwent unsuccessful secondary MRND.
†One patient underwent unsuccessful secondary MRND.
‡One patient underwent successful MRND shortly postoperative.
§As well as removal of pre- and paratracheal nodes.
‖One patient in both groups underwent unsuccessful secondary MRND.

diastinal compartments (Table 2). From 1983 on, we adapted a compartment-oriented approach in lymph node dissection, which implies that a microdissection was done of the central compartment, and MRND was performed on the side(s) where positive lymph nodes were found. Eight times only the pre- and paratracheal nodes were taken out, because these patients had no macroscopically suspicious lymph nodes; MRND was done once at primary operation.

In group 2, 26 patients underwent a (near-)total thyroidectomy; in one patient the operation was locally not radical. Type of lymph node surgery was basically the same as in group 1; in this group two patients had MRND, and in 13 cases only the central nodes were removed.

CT was measured by means of a radioimmunoassay which was developed in our own department (15); from 1984 on, a commercial kit (Byk/Sangtec, Dietzenbach, Germany) was used, which gave comparable results (16).

Patients in the MEN 2 families were identified by demonstration of a clearly elevated stimulated calcitonin (SCT) 2 or 5 minutes after pentagastrin provocation with 0.5 µg/kg body weight intravenously (normal SCT < 40 pmol/L) or an elevated basal calcitonin (BCT) level (normal BCT < 14 pmol/L). Patients were called converters if they initially had normal CT levels which rose to elevated CT levels during follow-up. For postoperative follow-up, a pentagastrin test was repeated shortly after surgery, after three months, after one year, and thereafter every year. If BCT was clearly and repeatedly abnormal, further pentagastrin testing was usually omitted. "Normal CT levels" means both BCT and SCT are normal. "Elevated CT levels" may refer to either SCT alone or, as was the case in most of the patients, both BCT and SCT.

Results

Outcome of primary treatment

Twenty-five patients in group 2 and 12 patients in group 1 had an elevated CT level preoperatively. In six patients, among them two index cases in group 2, preoperative CT levels were not known (Table 1).

Five patients in group 1 and 12 patients in group 2 were found to have normal CT levels postoperatively (Table 2). In these patients usually only the central lymph nodes had been removed; in two patients in group 2 a limited lateral dissection by picking out of suspicious nodes (which on histological examination proved to contain no tumor) was done and one patient in this group had a single lymph node biopsy only. In both groups all but one of the patients with normal postoperative CT levels appeared to be node-negative (Table 3). The one patient in group 1 who underwent a unilateral MRND because of one positive paratracheal node appeared to have no further lymph node metastases. Afterwards he suffered neurapraxia of the hypoglossal nerve, as well as impaired shoulder function. The apparently cured node-positive (N1) patient in group 2 only underwent bilateral picking out of nodes. In the apparently node-negative (N0) group, postoperative CT levels remained elevated in some patients: three in group 1 and four in group 2. Also in group 2, two patients with initially normalized CT levels (one with homolateral lymph node metastasis, one node-negative) showed an increasing CT level after several years (Table 4). On the other hand, one N1 patient in group 2 demonstrated spontaneous late normalization of CT levels (Figure): BCT remained normal after two years, SCT remained less than 40 pmol/L after three years and became undetectable after seven years. Of the two patients who underwent primary MRND in this group, one developed a persistent hypoparathyroidism.

Secondary treatment

Of the four patients in group 1 in whom only central lymph nodes were removed and who had elevated postoperative CT levels, one had additional MRND. Also, three patients (in whom lymph node surgery at primary operation was limited to taking a biopsy which on histological examination proved to contain tu-

♀ 44 yrs, $pT_4-N_1-M_0$
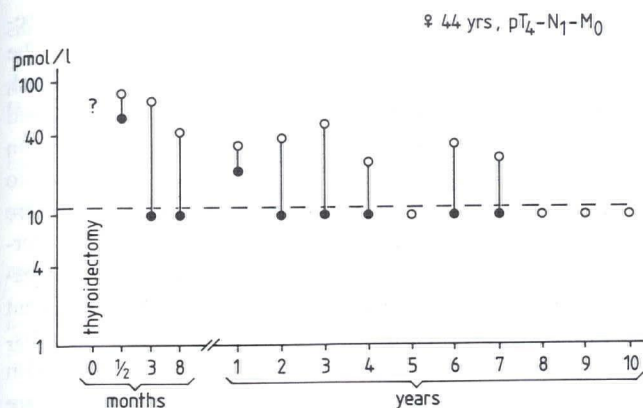
Figure—Follow-up CT levels in one patient who showed spontaneous normalization after more than seven years. Solid circles = basal CT, open circles = stimulated CT.

mor) underwent secondary MRND. Unfortunately, despite removal of tumor-positive nodes, MRND was not successful in any of them. CT levels did not normalize, and the patients died during follow-up (Tables 2 and 4). Postoperatively, one patient had diminished shoulder function due to damage of the accessory nerve and one patient had bilateral and two unilateral paralysis of the vocal chords. One of these also had a large hemorrhage in the operative field.

In group 2, one N1 patient with a high postoperative CT level underwent additional bilateral MRND immediately after primary operation, whereafter CT normalized. Two positive lymph nodes containing micrometastases were found in the dissection material. In two other patients who had secondary MRND seven and eight years after primary operation because of increasing BCT, the intervention was less successful with CT levels failing to normalize afterwards. There were no serious complications after MRND in this group.

Survival and long-term follow-up

In group 1, only four patients were still alive in 1991, a mean of 12.3 years after operation (range 8 to 16 years). These patients all had normal postoperative CT values (Table 4). One of them had undergone an MRND because of one homolateral positive lymph node (Table 2); the others were node-negative. Twelve patients in this group died after a mean of 38 ± 25 months; eight died of the disease, three of unknown causes (in one of them probably old age), and one patient with normal postoperative CT died of a metastasized breast carcinoma without evidence of MTC.

In group 2, only one patient died of the disease with extensive liver and bone metastases nine years after operation. He had elevated CT levels after operation. The other 26 patients are alive after a mean follow-up of 11 ± 1.8 years (range 8 to 16 years). Twelve of them have normal CT levels and are doing well, among them two patients who initially had elevated postoperative CT levels: one with spontaneous conversion (Figure) and one with normalization after additional MRND shortly after primary operation. Fourteen patients presently have elevated CT

Table 3
Lymph Node Stage in Relation to Postoperative CT Level

| | Group 1 | | Group 2 | |
	CT Normal	CT Elevated	CT Normal	CT Elevated
N0	4	3	11	4
N1	1	8	1	11
Total	5	11	12	15

Table 4
Latest CT Levels at Follow-up in Relation to Postoperative CT Levels

| | Group 1 | | Group 2 | |
	CT Normal	CT Elevated	CT Normal	CT Elevated
Latest follow-up:				
CT level normal	5*	—	10	2
CT level elevated	—	11†	2	13‡
Total	5	11	12	15

*One patient died of metastastized breast carcinoma.
†All died during follow-up.
‡One patient died with extensive lymph node, liver, and bone metastasis of MTC.

levels, including two patients who had normal CT levels immediately after operation, the two with primary MRND, and the two with additional MRND several years after primary operation. Of these 14, six patients have BCT levels of more than 400 pmol/L. One of them has residual local tumor as well as liver metastases; one already had histologically proven liver metastases in 1964, 15 years before her thyroid operation (17), and is clinically not deteriorating; and one seems to have rapidly progressive liver metastasis. In the other three, as well as in the eight patients with BCT levels between 14 and 400 pmol/L, no other evidence of metastasis is currently demonstrable.

Discussion

In this retrospective study we have tried to assess the value of MRND in patients with MTC in our clinic by reviewing the outcome of the patients operated on from 8 to 16 years ago. At that time, it was not the usual practice to perform elective MRND, so we do not have enough data to draw valid conclusions on its efficacy from our material. Our results therefore are limited to the outcome of secondary MRND, as well as long-term follow-up of those patients who did not undergo MRND.

A large difference in survival was seen between our two groups. There are two reasons for this. First, five-year survival in group 1 was in fact dramatically low compared to rates reported in the literature (1), probably because several patients in group 1 were of an advanced age at the time of diagnosis (four patients were well over age 75 years). Second, tumor stage was more advanced in group 1; all patients presented with a palpable swelling, and in three a radical operation was no longer possible. Another difference between the two groups was that a normal

postoperative CT level in group 1 was clearly related to a good prognosis, whereas in group 2 this was less evident because two patients showed late conversion to elevated levels and one patient showed spontaneous normalization. In other words, CT levels in group 2 followed a much less predictable course than in group 1.

Because in our MEN 2 group there were four patients (among them one so-called converter) apparently without lymph node involvement who were found to have elevated postoperative CT levels (Table 3), it would be tempting to conclude that a primary elective bilateral MRND should be done in all MEN patients regardless of lymph node stage. However, our data seem to indicate a better correlation of treatment success with lymph node stage than with the extent of lymph node dissection; in none of our patients with normal postoperative CT levels could this be attributed to an extensive primary lymph node dissection (Tables 2 and 3), while on the other hand none of the patients with extensive lymph node involvement (i.e., more than five positive nodes) became tumor-free. This corresponds with the findings of Samaan et al (18) who studied a group of patients with MTC limited to the thyroid (N0) and found no difference in outcome between those who had or did not have MRND. Furthermore, Russell et al (8) found no difference in survival in the group with an advanced tumor stage between the patients who were treated with a limited operation and those who had a more radical lymph node resection.

The clinical course of our patients with elevated CT levels tends to be benign: few patients have symptoms, few patients have demonstrable tumor, and only one patient has died. This "dormant course" of the tumor has also been reported by others (10,19). Still we must keep in mind that these are young patients and overall life expectancy may be reduced; tumor metastasis might be detected many years after operation.

At present, treatment of tumor relapse and especially of metastasis is not satisfactory (20-23), although promising results have been seen with ^{131}I MIBG (24).

Normalization of CT levels has been reported after removal of residual lymph node metastases localized to the neck by careful secondary MRND (14,25), but no data on long-term follow-up are available yet. Looking closely at the results of Tisell et al (14), it is remarkable that only patients with six or less positive nodes at secondary dissection were cured. Several other authors report less favorable results (10,19,26,27), although this may partly depend on a difference in technique and patient selection. Raue et al (26) saw a better 5-year survival rate in their group with reintervention, although only twice was normalization of CT levels obtained; however, their groups do not appear to be comparable because in the group without reintervention there were six patients with an advanced stage of the disease. Low success rates at secondary MRND might also be due to (occult) hepatic metastases, which have been shown to occur early in the course of the disease (28). This could also be the explanation for our finding that several apparently node-negative patients turned out to have elevated CT levels postoperatively.

In conclusion, although several authors advise primary elective MRND in patients with MTC, our data do not support these recommendations. None of our patients became CT-negative as a result of extensive primary lymph node surgery, but rather because of a favorable tumor stage. CT levels in all but two of the patients with normal postoperative CT levels remained normal, and one patient with elevated postoperative CT even showed spontaneous normalization. In our material, only one of seven secondary MRNDs was successful; this patient was found to have two additional positive nodes. Many complications were seen after MRND. Nevertheless, in the absence of effective therapies other than surgery, there seems to be a small group of patients who potentially benefit from curative MRND. To prevent overtreatment, we would advise a systematic lymph node dissection of the central compartment at primary operation, with extension towards an MRND only if (micro)metastases are identified. If postoperative CT levels remain elevated in patients who did not undergo extensive primary lymph node dissection, additional (secondary) MRND should be considered. The value of this procedure remains unproven. In our opinion, it is questionable whether extensive lymph node surgery improves survival of patients with extensive (e.g., ten or more) lymph node metastases.

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